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STRUCTURAL CHANGES IN THE LIVER IN EXPERIMENTAL CHRONIC HEPATITIS AND ITS CORRECTION BY BENZONAL

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KEY WORDS: structure of the liver; chronic hepatitis; correction

The essence of the problem of reversibility of pathological changes in the liver is stimulation of regeneration, and its solution depends on the level of cellular and intracellular repair processes [3]. The search is currently in progress for new and effective preparations which will stimulate regeneration of the liver when affected by chronic disease. The anticonvulsant drug benzonal, a barbituric acid derivative with a stimulating effect on activity of the microsomal enzymes of the liver, is particularly valuable in this respect and has been accepted by the pharmacologic committee of the USSR for wide use in the treatment of liver diseases.

EXPERIMENTAL METHOD

Experiments were carried out on 30 male albino rats divided into three groups. Animals of group 1 were intact, in animals of group 2 experimental chronic hepatitis was induced by injection of CCl_4 twice a week for 60 days in a dose of 2 mg/kg body weight; in the animals of group 3 experimental chronic hepatitis also was induced but they were treated with benzonal in a dose of 50 mg/kg for 10 days. Liver sections were stained with hematoxylin and eosin and by histochemical reactions (PAS, for RNA, by Brachet's method). The material was studied in the electron microscope by a morphometric method. The number of binuclear cells and mitoses to every 10,000 hepatocytes was calculated, and areas of necrosis were determined planimetrically.

EXPERIMENTAL RESULTS

Marked structural changes were discovered in the liver of the animals of group 2 in the form of swelling of the trabecular structure, static congestion of the vessels, and degenerative and necrotic changes. Destruction of the limiting membrane by lymphohistiocytic infiltration led to the development of foci of periportal necrosis, with the appearance of pale patches, occupying a considerable area, as a result of reduction of the RNA and glycogen content (Table 1). Similar changes constitute the picture of active chronic hepatitis of virus etiology [2, 6, 7]. Electron-microscopic examination revealed disturbances of the fine structure of the hepatocytes. In most of them the number of tubules of the smooth (SER) and rough

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TABLE 1. Area of Necrotic Foci, Number of Binuclear Cells and Mitoses in Liver in Chronic Hepatitis before and after Treatment by Benzonal (M ± m)

Group of animals		Area of foci of necrosis, conventional units	Number of binuclear cells	Number of mitoses
1	(control)	0	1,0±0,09	0,003±0,0003
3	before treatment	39,8±0,9	2,2±0,09	0,002±0,0005*
	after treatment	7,0±1,85	2,7±0,1	0,009±0,001

Legend. *p > 0.05.

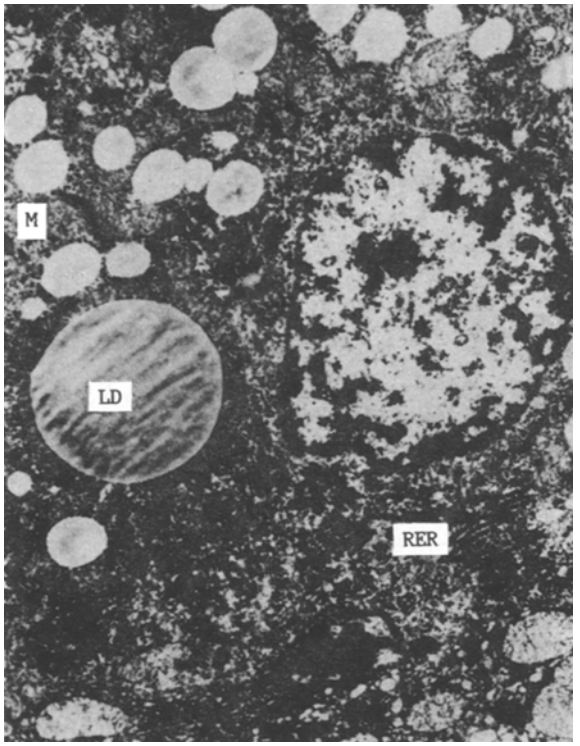

Fig. 1. Experimental chronic hepatitis. Decrease in number of mitochondria (M), swelling and clearing of matrix of some of them. Reduction of elements of RER and disturbance of its juxtamitochondrial location. Many lipid droplets present (LD). Magnification: 10,000.

endoplastic reticulum (RER) was reduced. The mitochondria were swollen with a translucent matrix and with disoriented cristae. Many lipid drops and lipofuscin granules also were observed (Fig. 1).

Besides degenerative changes [1], compensatory and adaptive processes developed in the chronically diseased liver. This was shown by an increase in the number of binuclear (Table 1) and hypertrophied cells, with high synthetic activity, as was confirmed by an increase in the number and size of the ribosomes and polysomes and large mitochondria with an electron-dense matrix, in their cytoplasm and by their clearly visible cristae, surrounded by elements of the RER. The mitotic activity of the hepatocytes showed no significant change compared with the control (Table 1).

After administration of benzonal to the animals with chronic hepatitis (group 3), besides normalization of the trabecular structure, other changes included a marked decrease in area of the necrotic foci (Table 1), resorption of the proliferating connective tissue, and preservation of lobules at the periphery with fatty degeneration, in the form of large droplets.

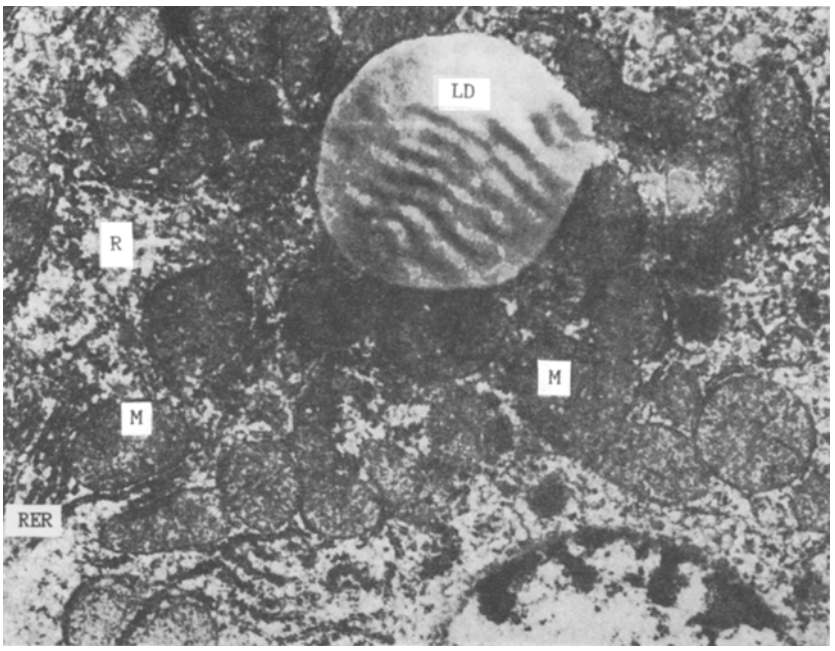

Fig. 2. Administration of benzonal. Electron-dense mitochondria (M), surrounded by elements of RER, are present in different sizes. Numerous ribosomes (R), polysomes, and large lipid droplets (LD) present. Magnification: 10,000.

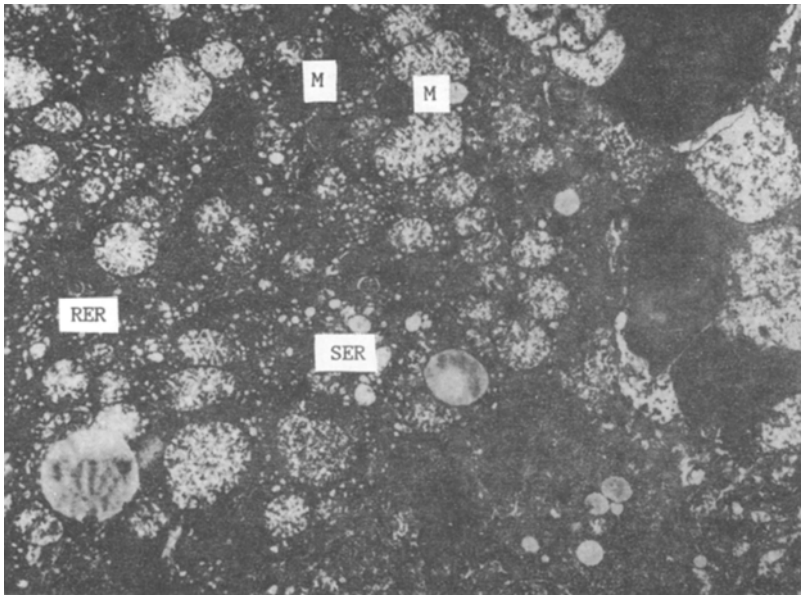

Fig. 3. Administration of benzonal. Besides small, electron-dense mitochondria (M) many large, swollen mitochondria with translucent matrix also are present. Many vesicles and tubules of the SER present among elements of the RER. Magnification: 5000.

Normalization of the structure of the liver was accompanied by an increase in the number of mitoses (cellular regeneration), and also by an increase in the number of binuclear and hypertrophied cells (intracellular regeneration [3]). Two types of cells were predominant. Those of one type, more electron-dense, were characterized by large mitochondria with a dense matrix and clearly distinguishable cristae, surrounded by elements of the RER and containing many free ribosomes and polysomes, glycogen granules and large lipid drops (Fig. 2). Hepatocytes of this kind correspond to the "dark cells" in a state of potential function, and whose

marked hyperplasia and hypertrophy of the mitochondria are evidence of an increase in their energy-producing ability [4]. Hepatocytes of the second type appeared less electron-dense because they contained structureless zones, as well as swollen mitochondria with translucent matrix and disoriented cristae. The cytoplasm also contained mitochondria with a denser matrix and with regularly oriented cristae. The most characteristic feature of these cells was the development of elements of the RER and SER. In some places transition of the RER into the SER was observed, accompanied by removal of ribosomes from the membranes (Fig. 3). Considering that the function of SER is to take part in metabolism of foreign chemical substances [5], we consider that the most important role of these cells is to weaken the action of toxic metabolites on the affected liver.

The results of these investigations thus show that repair processes in chronic hepatitis cannot compensate for the death of large areas of the parenchyma. Administration of benzonal promotes the reversibility of the process due to the considerable activation of cellular and, in particular, of intracellular processes, as is confirmed by the presence of cells of two types: cells with enhanced energy potential, and cells eliminating toxic metabolites more quickly.

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EXPERIMENTAL CANDIDIASIS OF THE ORAL MUCOSA DURING INHIBITION OF LEUKOPOIESIS

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The number of patients with visceral forms of candidiasis has risen steadily in recent years, probably due both to the widespread use of modern therapeutic substances and to the prevalence of severe underlying diseases on the basis of which this mycotic condition frequently develops [3-5, 7]. The tissue response to introduction of conditionally pathogenic fungi of the *Candida* genus has a wide spectrum of morphological manifestations [4-7], and the predominance of an acellular inflammatory reaction in a certain category of patients is probably linked with the corresponding immune status. Acellular or inert inflammation is characterized by the absence of typical inflammatory cells within the pathological focus. An important component of this type of reaction may be necrosis [6]. However, the morphology and morphogenesis of this variant of inflammation have not been adequately studied.

In the investigation described below, on an experimental model of candidiasis of the oral mucosa accompanying administration of the antibiotic tetracycline and the cytostatic vinblastine sulfate, the character of development of the acellular inflammatory reaction was studied at the tissue and ultrastructural levels.

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